

FMR1-RELATED DISORDERS

FMR1-related disorders include fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and FMR1-related primary ovarian insufficiency (POI). Fragile X syndrome affects approximately 1 in 4,000 males and 1 in 8,000 females characterized by moderate to severe intellectual disability, macroorchidism, and distinct physical features. Early signs include delayed speech and language. Behavioural characteristics can include autism, hyperactivity and poor eye contact. Physical features, such as a long face and large or prominent ears, are usually more noticeable in adults than children. FMR1-related POI is defined as cessation of menses before age 40 years and FXTAS is characterized by progressive problems with movement (ataxia), tremor, memory loss, loss of sensation in the lower extremities (peripheral neuropathy), and behavioural changes. About 20% of women with POI and 30% of men (and some women) with FXTAS carry a premutation.

GENETICS & DISORDER MECHANISMS

FMR1-related disorders are X-linked and caused by abnormal function of the FMR1 gene located on the long arm of chromosome X. Fragile X syndrome is caused by a full mutation or other loss of function variant that causes loss of expression of the FMR1 gene. In most cases fragile X syndrome is caused by the unstable expansion of the trinucleotide sequence CGG located in the 5' UTR of the FMR1 gene. The abnormal expansion of this triplet leads to hypermethylation and consequent silencing of the FMR1 gene with decreased protein levels in the brain. The trinucleotide repeat is inherited in an unstable fashion in fragile X families and displays intergenerational expansions. FMR1 premutations are not associated with fragile X syndrome but do convey risk for POI and FXTAS, which are caused by a toxic gain of function of the FMR1 transcripts. Women carrying a premutation are at risk of having offspring with a full mutation.

WHO SHOULD BE TESTED?

- Individuals of either sex with Intellectual disability, developmental delay, and autism, especially if they have (a) any physical or behavioural characteristics of fragile X syndrome, (b) a family history of FMR1-related disorders, or (c) male or female relatives with undiagnosed intellectual disability.

- Individuals seeking reproductive counselling who have (a) a family history of FMR1-related disorders, or (b) a family history of undiagnosed intellectual disability.
- Fetuses of known premutation carrier females.
- Individuals of either sex >50 years of age who have progressive cerebellar ataxia and intention tremor with a positive family history of FMR1-related disorders in whom other common causes of ataxia have been excluded
- Women with unexplained POI.

TEST METHODS

PCR amplification using the Asuragen AmplideX[®] FMR1 PCR kit to detect alleles in the normal, intermediate, premutation and full expansion (>200 CGG repeats) range. This assay will size alleles up to 200 CGG repeats. Repeats greater than 200 CGG repeats will be reported as a full expansion.

TEST SENSITIVITY

All cases of FRAXA caused by CGG expansion will be detected by this assay (~99% of patients with FRAXA). Rare cases (~1% of patients with FRAXA) are caused by mutations within the FMR1 gene and will not be detected by this assay.

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

| Repeat size | # of CGG repeats | Clinical Phenotype | Transmission |
|---------------|------------------|---------------------|--|
| Normal | ~5 to 44 | None | Stably transmitted |
| Intermediate | ~45 to 54 | None | May increase in size in subsequent generations |
| Premutation | ~ 55 to 199 | Risk of POF & FXTAS | Risk of expansion to full mutation |
| Full mutation | Over 200 | Symptoms of FRAXA | |

For More Information

The National Fragile X Foundation
www.fragilex.org

Online Mendelian Inheritance in Man: <https://www.omim.org/> Items # 300624, #31360, #300623

Gene Reviews:
<https://www.ncbi.nlm.nih.gov/books/NBK1384/>

Genetic Testing Registry online clinical information resource <https://www.ncbi.nlm.nih.gov/gtr/conditions/C0016667/>

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the

National Society of Genetic Counsellors website at www.nsgc.org

SickKids Genomic Diagnostics Laboratory: www.sickkids.ca/genome-diagnostics



1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of Fragile X.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.